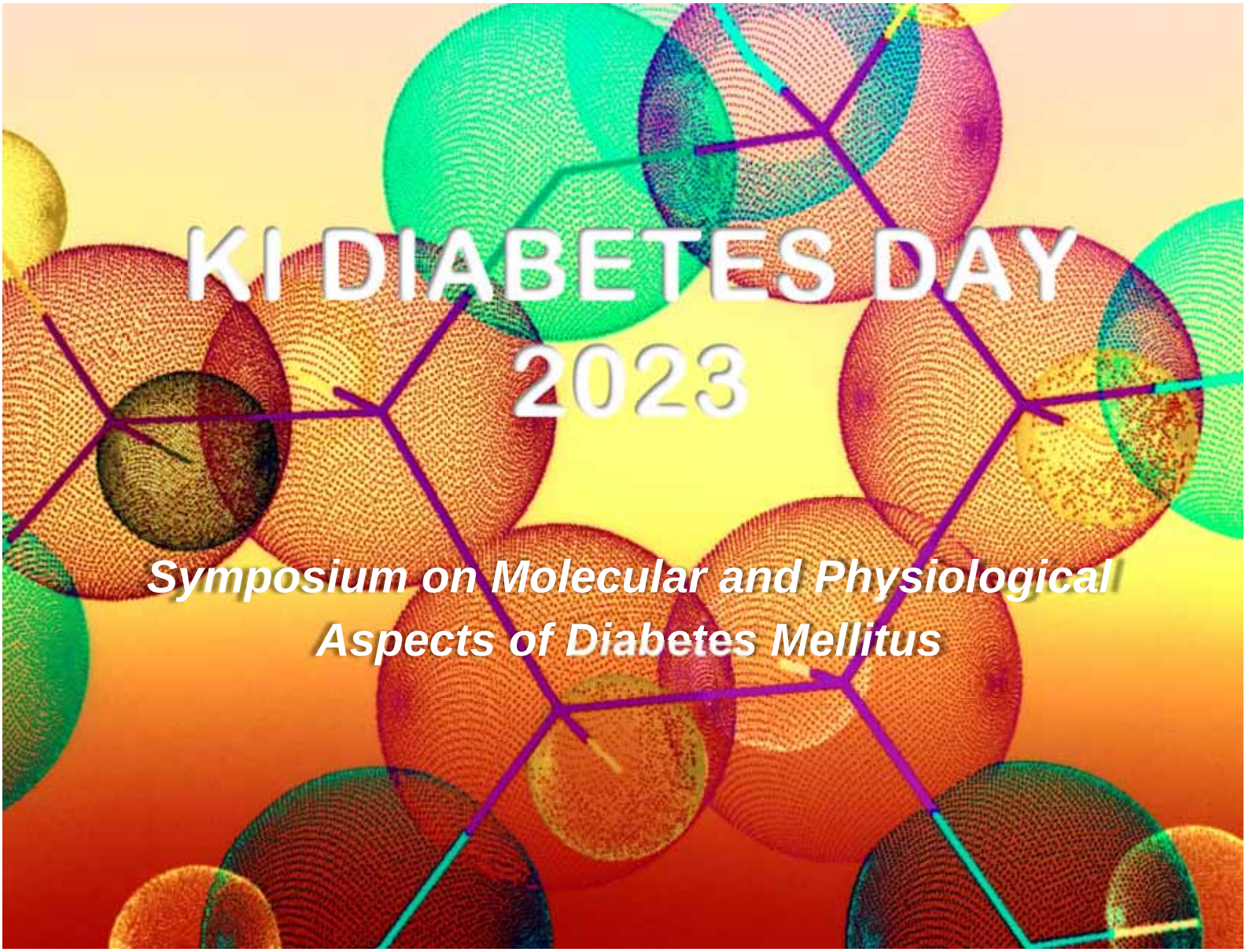

November 14, 2023 | Karolinska Institutet

PROGRAMME AND ABSTRACTS

world diabetes day

SRP DIABETES

Karolinska Institutet

Organiser:

Strategic Research Programme in Diabetes at Karolinska Institutet (SRP Diabetes).

https://ki.se/en/srp-diabetes

SRP Diabetes is an integrated research environment in the diabetes and metabolism area with some 400 affiliated researchers at both Karolinska Institutet and Umeå University. Results are translated between basic and clinical science with the aim to improve both prevention, care and treatment of people with diabetes.

Specifically, SRP Diabetes activities aim to:

- Support technical platforms important for the whole research programme. These platforms include a Metabolic Phenotyping Centre for Diabetic Animal Models, a Centre for Clinical Metabolic Research in Diabetes, Beta Cell in-vivo Imaging/ Extracellular Flux Analysis (Seahorse) and support for Spatial transcriptomics.
- Support critical instrumentation to consolidator level group leaders
- Support the next generation of scientist: postdoctoral fellowship program
- Increase interactions between the research teams of the programme by supporting collaborative projects and arranging common symposia, meetings and seminars
- Support undergraduate and graduate education within the research areas connected to the programme
- Increase translational research by supporting collaborative projects between experimental and clinical researchers
- Facilitate international contacts
- Increase interactions with the biotech and pharmaceutical industry
- Support innovation and commercial utilization by liasing with Karolinska Institutet Innovations
- Increase public awarness and inform about current diabetes related research

The programme coordinates laboratories possessing substantial expertise and unique technical resources, thus affording a natural point of contact for collaboration within the diabetes area, both for researchers within Karolinska Institutet and Umeå University as well as with external researchers.

SRP Diabetes Management:

Director: Anna Krook (Karolinska Institutet)

Vice-Director: Olov Andersson (Karolinska Institutet)

Helena Edlund (Umeå University)

Malin Flodström Tullberg (Karolinska Institutet)

Erik Näslund (Karolinska Institutet)

Mikael Rydén (Karolinska Institutet)

Harriet Wallberg (Karolinska Institutet)

Venue: Eva & Georg Klein seminar hall, Biomedicum, Karolinska Institutet, Solna campus

Web/Twitter: https://ki.se/en/srp-diabetes/diabetes-day / @srp_diabetes

Programme

08:30 – 09:00	REGISTRATION
09:00 - 09:10	Welcome Note: **Anna Krook**
SESSION 1	**Circadian Rhythms and Metabolism** — **Chair: Harriet Wallberg**
09:10 - 09:45	"(Lifestyle) Interventions to combat type 2 diabetes: a 24/7 job?" **Patrick Schrauwen,** *Maastricht University*
09:45 - 10:20	"Circadian clock in skeletal muscle: critical component of glucose homeostasis and metabolic flexibility" **Karyn Esser,** *University of Florida*
10:20 - 10:50	COFFEE BREAK
SESSION 2	**Regulation of Metabolism in Health and Disease** — **Chair: Helena Edlund**
10:50 - 11:25	"Metformin targets mitochondrial complex I to regulate physiology and disease" **Navdeep Chandel,** *Northwestern University*
11:25 - 12:00	"Metabolic regulation of insulin secretion in health and disease" **Frances Ashcroft,** *University of Oxford*
12:00 - 13:00	LUNCH (Posters to be mounted)
SESSION 3	**Type 1 Diabetes** — **Chair: Malin Flodström Tullberg**
13:00 - 13:35	"Leveraging new knowledge from the human pancreas to advance and improve understanding and treatment of Type 1 diabetes" **Sarah Richardson**, *University of Exeter*
13:35 - 14:10	"The Ailing Beta Cell in Type 1 Diabetes: Insights from a Trip to the "ER" **Carmella Evans-Molina**, *Indiana University*
14:10 - 14:40	COFFEE BREAK
SESSION 4	**Systemic Energy Homeostasis** — **Chair: Mikael Rydén**
14:40 - 15:15	"Novel Insights into GIP Regulation of Energy Metabolism" **Timo Müller**, *Helmholtz München*
15:15 - 15:50	"Uncovering Novel GPCR Pathways for the Treatment of Obesity and Type 2 Diabetes" **Zach Gerhart-Hines,** *University of Copenhagen*
15:50 - 16:00	Closing Remarks: **Olov Andersson**
POSTER SESSION, Drinks and light bites	
16.00-18.00	Drinks and light bites served in the foyer by the entrance
16.15-16.45	Posters with odd numbers will be presented
16.45-17.15	Posters with even numbers will be presented

Speaker abstracts

SESSION 1

(Lifestyle) interventions to combat type 2 diabetes: a 24/7 job?

Patrick Schrauwen

Department of Nutrition and Movement Sciences, NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, 6200 MD, Maastricht, The Netherlands.

Recently our 24-hour culture has been identified as another lifestyle factor that can cause type 2 diabetes. Technological and societal advances such as electric lighting and digital screens – leading to light exposure that is too dim during the day and too bright during the evening –, shift work, time zone transfers, and round-the-clock food availability disrupt our intrinsic and evolutionarily preserved 24-hour rhythms resulting in a desynchronization between light cues and behavior cues to our circadian system. This mistiming of cues is now thought to be a large contributor to the current metabolic health crisis, a concept known as circadian misalignment. Our internal biological clock sets circadian rhythmicity of a large range in bodily functions, including energy metabolism. We have shown that whole body energy expenditure and skeletal muscle mitochondrial function displays 24h rhythmicity in humans, a rhythm that is disturbed in prediabetic volunteers. Also, we have shown that a rapid day-night shift can lead to insulin resistance. More recently, we showed that also muscle metabolism shows 24h rhythmicity in healthy humans.
Next to light, also food and activity can function as zeitgebers for the molecular clock. Therefore, timing of interventions can be used to improve metabolic health; we and others showed that exercise training in the afternoon may have more beneficial effects compared to exercise training in the morning. Also, time restricted feeding improves rhythmicity of our metabolism and glucose homeostasis, and recent findings suggests that also light exposure can influence our 24h energy metabolism. Under healthy conditions, our 24h energy metabolism is aligned to periods of feeding and fasting and this fed-fasted cycle is disturbed in type 2 diabetes. This may also give rise to altered hepatic glycogen cycling, making depletion of hepatic glycogen stores a target to restore 24h substrate metabolism. In this lecture, the latest data on human interventions to restore 24h energy metabolism and the underlying mechanisms will be presented.

Speaker abstracts

Circadian clock in skeletal muscle: critical component of glucose homeostasis and metabolic flexibility

Karyn Esser

Professor and Chair, Co-Director, UF Claude D. Pepper Older American Independence Center, Department of Physiology & Aging, College of Medicine, University of Florida

Circadian rhythm disruptions resulting from shift work or lifestyle behaviors are now recognized as a modifier of metabolic health. The focus of this talk is on the role of the circadian clock mechanism in skeletal muscle as key component for muscle glucose homeostasis and metabolic flexibility. We used systemic adeno-associated virus delivery to restore the core clock gene, Bmal1, specifically in skeletal muscle fibers of Bmal1-KO mice. We found that rescue of Bmal1 in muscle only was sufficient to restore muscle strength and systemic glucose tolerance with no effects on muscle size, fiber area, or fiber composition. Multi-omics analyses determined that glucose metabolism was the key pathway restored following AAV delivery. Lastly, we determined that the improved metabolic flexibility in the muscle resulted in significant changes in metabolism and inflammation across several peripheral tissues including heart, liver, lung and white fat. These findings highlight the critical role of the circadian clock in skeletal muscle with significant implications for metabolic health.

Speaker abstracts

SESSION 2

Metformin targets mitochondrial complex I to regulate physiology and disease.

Navdeep S. Chandel

Northwestern University Feinberg School of Medicine, Chicago, IL 60657 USA

The major function of mitochondria in cellular homeostasis has been the generation of ATP through oxidative phosphorylation. However, we have previously demonstrated that mitochondria can serve as signaling organelles by releasing low levels of reactive oxygen species (ROS) that are essential for hypoxic activation of HIF, immunity, and cellular differentiation. Our recent findings indicate that mitochondria also release TCA cycle metabolites that are necessary for chromatin and DNA modifications to control stem cells and Tregs. Thus, mitochondrial electron transport chain (ETC) controls ROS and metabolite production to maintain health. Disruption of these signals can incur pathology. Interestingly, metformin's molecular target is mitochondrial complex I (NADH dehydrogenase) of the electron transport chain. To investigate this hypothesis, we created transgenic mice that conditionally expresses the yeast mitochondrial NADH dehydrogenase NDI1 protein that complements the loss of the 45-subunit mammalian mitochondrial complex I in mice. Metformin or other mitochondrial complex I inhibitors do not inhibit NDI1 protein function. Metformin was able to lower blood glucose levels in wild-type mice but not in whole body NDI1-expressing mice. Furthermore, metformin does not decrease tumor growth in cancer cells expressing NDI1 thus indicating metformin's anti-cancer mechanism of action involves inhibition of inhibiting mitochondrial complex I function. I will present our ongoing research on metformin's inhibition of mitochondrial complex I.

Speaker abstracts

Metabolic regulation of insulin secretion in health and disease

Frances Ashcroft

Professor, Department of Physiology Anatomy and Genetics, University of Oxford
Parks Road, Oxford, OX1 3PT

The ATP-sensitive potassium (KATP) channel plays a central role in insulin secretion in both health and disease. Glucose stimulates insulin secretion by enhancing intracellular ATP, which closes KATP channels, leading to electrical activity, calcium influx and insulin release. This process fails in diabetes. Gain-of-function mutations that impair KATP channel inhibition by ATP cause a rare inherited form of diabetes (neonatal diabetes). Their identification has enabled most patients to switch from insulin injections to sulphonylurea drugs (that block KATP channel activity) with considerable improvement in their clinical condition and quality of life. Type 2 diabetes (the most common form of diabetes) is characterised by chronic hyperglycaemia and a gradual decline in beta-cell function. We have employed a mouse model of inducible neonatal diabetes to look at the effects of chronic hyperglycaemia on beta-cell function.

Diabetes causes marked changes in metabolic gene and protein expression, as well as in metabolic enzyme activity, that lead to impaired oxidative metabolism and ATP production, and thus reduced insulin release. Diabetes also dramatically reduces insulin content and insulin gene expression. We postulate these changes result in a vicious spiral that drives the progression from impaired glucose tolerance to type 2 diabetes. We find only a small elevation of blood glucose is needed to initiate this effect. This talk will focus on how chronic hyperglycaemia impairs beta-cell metabolism and thereby drives beta-cell decline. Our studies show it is a glucose metabolite (rather than glucose itself) that is responsible and lead us to propose one possible pathway for how this metabolite impairs beta-cell function. They also suggest a potential novel therapy to reduce/halt beta-cell decline: reduce metabolic flux below glucokinase to that found under non-diabetic conditions. Our work is funded by the UK Medical Research Council.

Speaker abstracts

SESSION 3

Leveraging new knowledge from the human pancreas to advance and improve understanding and treatment of Type 1 diabetes

Sarah Richardson

Associate Professor in Cellular Biomedicine, Director of Postgraduate Research for Department of Clinical and Biomedical Sciences (DCBS), Exeter Centre of Excellence for Diabetes Research (EXCEED), University of Exeter

Type 1 diabetes (T1D) affects >413,000 people in the UK with incidence increasing 4% annually. Despite significant improvements in care and management, reliance is still placed on insulin replacement as a primary mode of therapy rather than on strategies to arrest or reverse disease progression, or strategies to replace functional beta cells. These strategies will only be possible with a more comprehensive understanding of disease processes in the target organ, the pancreas, which is difficult in situ. Over the last 16y, I have interrogated human pancreas using unique biobanks (a key one held in Exeter), and I have collaborated extensively with teams globally to expand our collective appreciation of the pathophysiology of the pancreas in T1D. This presentation will focus on describing these unique biobanks, their strengths and weaknesses and will explore what lessons have been learnt from their interrogation. Areas of focus will include exploring differences between individuals to better define distinct forms of T1D and examining strategies that beta cells may use to promote or resist immune attack. This knowledge will help guide treatment and prevention strategies and offer valuable translational insights to inform the development of beta-cell recovery and replacement approaches.

Speaker abstracts

The Ailing Beta Cell in Type 1 Diabetes: Insights from a Trip to the "ER"

Carmella Evans-Molina

Eli Lilly Foundation Professor of Pediatric Diabetes, Director, Indiana Diabetes Research Center, Indiana University

Type 1 diabetes (T1D) results from autoimmune destruction of the insulin-producing β cells of the pancreas, leading to hyperglycemia and metabolic dysregulation. Since the discovery of insulin over 100 years ago, T1D has evolved from a certain death sentence to a manageable chronic disease condition. However, the medical, economic, and mental health burden of disease is still pronounced. Our increased understanding of T1D disease pathogenesis has opened the door to an age of early disease identification, modification, and prevention. In my talk, I will present two vignettes from the lab that have advanced our ability to identify and modify T1D sequelae. First, we used unbiased small RNA sequencing in human islets and islet-derived extracellular vesicles to identify a signature of micro(mi)RNAs that may serve as biomarkers of T1D. Importantly, we found that a subset of these miRNAs is upregulated in the serum of children with new-onset T1D and in pancreatic sections from cadaveric donors with autoantibody positivity or T1D. Second, we showed that pharmacological inhibition of tyrosine protein-kinase 2 (TYK2), a downstream mediator of IFNα signalling, decreases pancreatic islet inflammation and delays disease onset in two preclinical mouse models of T1D. These findings indicate that inhibition of TYK2 signaling could have efficacy for the prevention of T1D in at-risk individuals or the treatment of those with new-onset disease. I will conclude my talk by sharing my vision for the future of diabetes care, where multiple biomarkers of β cell stress may be combined with additional immune and metabolic biomarkers to better predict disease risk and to improve therapies to prevent or delay T1D development.

Speaker abstracts

SESSION 4

Novel Insights into GIP Regulation of Energy Metabolism

Timo Müller

Acting Director and Head of Div. of Molecular Pharmacology, Institute for Diabetes and Obesity, Helmholtz München

The development of unimolecular co-agonists for the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors represents a significant breakthrough in addressing obesity and type 2 diabetes. Nevertheless, while it has been demonstrated that GIPR:GLP-1R co-agonism is more effective in reducing body weight compared to using GLP-1R agonists alone in both preclinical and clinical studies, the specific role of GIP in controlling energy metabolism remains enigmatic. In recent years, our research has revealed that long-lasting GIPR agonists function centrally to reduce body weight by suppressing food intake. Additionally, we have recently pinpointed the specific neural populations through which GIP acts in the brain to regulate feeding, demonstrating that GIPR agonism is a crucial component of the GIPR:GLP-1R co-agonists in the regulation of body weight. Furthermore, our findings have shown that tirzepatide has effects that vary by species, favoring the GLP-1 receptor in mice but the GIP receptor in humans. In summary, our work underscores the significance of GIPR agonism in the control of energy metabolism, paving the way for targeting the brain's GIP system through pharmaceutical means in the development of next-generation anti-obesity medications.

Speaker abstracts

Uncovering Novel GPCR Pathways for the Treatment of Obesity and Type 2 Diabetes

Zach Gerhart-Hines

Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen

Obesity and related cardiometabolic diseases are global crises that threaten to cripple healthcare infrastructures. These disorders originate from an excess calorie burden caused by consuming too much food and expending too little energy. Yet despite the latest advances in obesity pharmacotherapies, weight-lowering drug treatments currently only reach half the efficacy of surgical interventions in individuals living with both obesity and type 2 diabetes (T2D). We seek to identify means of boosting energy expenditure or metabolic rate to improve the next generation of biopharmaceuticals. We focus our efforts on the highly druggable G protein coupled receptors (GPCRs) to uncover novel solutions. Previously, we showed that the orphan receptor, GPR3, was a powerful activator of energy expenditure through adipose thermogenesis (Sveidahl Johansen et al, 2021). Most recently, we found that activation of Neurokinin 2 Receptor (NK2R) is sufficient to both increase energy expenditure peripherally and suppress appetite centrally. We focused on NK2R after discovering its significant genetic links to obesity and glucose control. However, therapeutically exploiting NK2R signaling has previously been unattainable because its endogenous ligand, Neurokinin A (NKA), is short-lived and lacks receptor specificity. Therefore, we developed selective, long-acting NK2R agonists, with potential for once-weekly administration in humans. In mice, these agonists elicit weight loss by inducing energy expenditure and non-aversive appetite suppression that circumvents canonical leptin signaling in addition to enhancing insulin sensitization. We identified a distinct neuronal population in the nucleus of the solitary tract (NTS) that controls energy homeostasis in response to NK2R agonism. In diabetic, obese nonhuman primates, NK2R activation is well-tolerated and significantly decreases body weight, blood glucose, triglycerides, and cholesterol, and ameliorates insulin resistance. These findings identify a single receptor target that leverages both energy-expending and appetite-suppressing programs to improve energy homeostasis and reverse cardiometabolic dysfunction across species.

Poster abstracts

Presenter Name	Poster nr
Butrym, Marta	P2
Byvald, Fabian	P1
Chang, Roger	P25
Collado Sanchez, Aida	P22
Dumral, Özge	P10
Incedal Nilsson, Ceren	P6
Jollet, Maxence	P13
Josyula, Vijay Sai	P8
Karadimou, Glykeria	P24
Kontidou, Eftychia	P23
Krämer, Niels	P18
MacGregor, Kirstin	P12
Maestri, Alice	P19
Matuseviciene, Lina	P9
Norlin, Stefan	P4
Ovezik, Maria	P5
Parajuli, Anirudra	P3
Sánchez-Ceinos, Julia	P20
Sinha, Neha	P7
Solinas, Giovanni	P16
Stocks, Ben	P14
Swaich, Jasmin	P21
Torstensson, Sara	P15
Waara, Erik	P11
Westerberg, Leo	P17

There are 25 posters to be presented in the foyer/hallway area by the main entrance to Biomedicum.

Poster screens are 145 cm high and 115 cm wide. Materials to attach with will be available.

Presenters of posters with odd numbers will be at their posters 16.15-16.45

Presenters of posters with even numbers will be at their posters 16.45-17.15

Posters to be mounted latest during lunch break.

Poster abstracts

P1 Fabian Byvald

Type III interferons are expressed in human pancreas at type 1 diabetes onset and induce immunostimulatory and antiviral activities in human beta cells

Ringqvist, E (1), Tuomela, S (1), Mazur, M (1), Byvald, F (1), Burdsall, K (1), Vasylovska, S (5), Parajuli, A (1), Sork, H (1), Krogvold, L (4), Dahl-Jorgensen, K (4), Matthews, C (3), Lau Börjesson, J (5), Gerling, I (2), Flodström Tullberg, M (1)

1. Center for Infectious Medicine, Dept. Medicine HS, Karolinska Institutet, Stockholm, Sweden.
2. University of Tennessee Health Science Center, VA Medical Center, Memphis, Tennessee, USA.
3. Current affiliation: College of Medicine Department of Pathology, University of Florida, Gainesville, Florida, USA
4. Unit Endocrinology and Diabetes, Department of Paediatrics, Oslo University Hospital Ullevål, Norway
5. Department of Medical Cell Biology, Uppsala University, Sweden.

Type 1 diabetes (T1D) results from progressive dysfunction and loss of insulin production by pancreatic islet β-cells. Coxsackievirus infections are more commonly present in children who develop T1D. The anti-viral immune response may contribute to β-cell destruction in human type 1 diabetes. Type III interferons (IFN-λ 1-4) constitute a group of IFNs that are produced by both immune and parenchymal cells during infection. We have previously shown that human pancreatic islets express type III IFNs when infected with Coxsackievirus B (CVB) in vitro. However, type III IFNs' role in T1D and direct effect on β-cells remains unexplored.
In the present study, we aimed to investigate if IFNλs are expressed in the human pancreas at diabetes onset and to describe the effects that IFNλ have on β-cells by in-depth proteome, islet transcriptome and immune marker analysis of a human β-cell line (EndoC-βH1), primary human islets and stem cell derived islet like clusters. We also investigated the function of IFNλ-induced pathways in β-cells regarding immune status and antiviral defense.

The proteome of IFNλ1- or IFNλ2-exposed EndoC-βH1 cells revealed 93 and 119 differentially expressed proteins. The cell surface expression of MHC class I was induced on both EndoC-βH1 cells and stem cell derived islet-like clusters, which was prevented by drugs blocking JAK/STAT signaling. IFNλ1/2 treatment strongly reduced permissiveness to CVB infection, as did blocking of the viral receptor (CAR). Finally, we discovered that the genes encoding IFNλ1/2 showed increased expression in islets from diabetic individuals compared to healthy controls.

In conclusion, we found that type III IFNs are expressed in the human pancreas at T1D onset. Type III IFNs increase MHC class I expression and activate antiviral defense in human β-cells. We also show that IFNλs have antiviral activity. In summary, these results highlight an immunomodulatory function of type III IFNs during T1D development.

Poster abstracts

P2 Marta Bytrum

Drug-repurposing as a strategy to identify new antivirals for addressing the role of enterovirus infections in type 1 diabetes

Marta Butrym[1], Marfa Blanter[1], Virginia Stone[1], Fabian Byvald[1], Svitlana Vasylovska[2], Joey Lau[2], Varpu Marjomäki[3], Malin Flodström-Tullberg[1]

[1] *Center for Infectious Medicine, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden*
[2] *Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden*
[3] *Department of Biological and Environmental Science, University of Jyväskylä, Jyväskylä, Finland*

Background and aims: Enteroviruses infecting via the gut have been linked to the development of type 1 diabetes (T1D). An association between prolonged faecal shedding of enterovirus and islet autoimmunity has been documented. Furthermore, enteroviral protein and genome have been identified in pancreatic islets of individuals with recent onset T1D, suggesting that an infection contributes to beta cell demise. To date, there are no antiviral drugs approved for the treatment of enterovirus infections. Drug repurposing can speed up the drug discovery process by finding a new clinical use for already approved drugs. In a previous drug repurposing screen, a drug Vemurafenib with unprecedented antiviral activity against several enteroviruses was found (Laajala et al.). The aim of this study was to investigate the efficacy of this drug in preventing infection of intestinal epithelial cells (IECs) and pancreatic beta cells by enteroviruses linked to T1D development.

Materials and methods: HeLa cells, the IEC line HT-29 and Caco-2, the pancreatic β cell lines INS-1 and iPSC derived islets (SC-islets) were treated with Vemurafenib or an analogue thereof (0-10 μM) with or without exposure to Coxsackie B viruses (CVBs). Cell viability was measured by trypan blue exclusion test. Virus infection and replication was assessed by flow cytometry and a standard plaque assay.

Results: A cancer drug Vemurafenib and its analogue in concentrations up to 10μM did not induce a cytotoxic effect in the tested cell lines. CVB infection and replication were dampened in drug treated cells and islets compared with vehicle-treated cells.

C**onclusions:** The tested drugs were found to have strong anti-enteroviral properties in vitro. Our studies suggest that this drug and its analogues should be further explored for their possible use as antiviral agents and treatment of enterovirus-induced disease.

Poster abstracts

P3 Anirudra Parajuli

Improving gut microbiome composition by environmental exposure as a measure to prevent type 1 diabetes

Parajuli, A. (1), Ringqvist, E. (1), Stone, V. (1), Castro, M. (1), Mäkelä, I. (2), Soininen, L. (3), Laitinen, O. (4), Sinkkonen, A. (2), Flodström Tullberg, M. (1)

1. Department of Medicine, Huddinge, Karolinska Institutet, Huddinge, Sweden,
2. Natural Resources Institute Finland, Horticulture Technologies, Turku, Finland
3. Department of Ecological and Environmental Science, University of Helsinki, Helsinki, Finland
4. Faculty of Medicine and Health Technology, University of Tampere, Tampere, Finland.

Urban lifestyle lacks natural stimuli for the human immune system, historically coming from exposure to nature and soil. Our recent study showed an inverse correlation between agricultural land cover and incidence of type 1 diabetes (T1D). This is in line with the biodiversity hypothesis which states that lack of nature interaction increases risk of allergic and autoimmune diseases by altering the gut microbiota and immune functions. Reduced abundance of beneficial bacteria like Lactobacillus is a risk factor in humans and experimental models of T1D. This study builds on the novel concept of the biodiversity hypothesis and aims to investigate the impact of early introduction to natural environment on the host microbiome with a future goal to evaluate its potential to prevent T1D. We utilized an in-house produced biodiversity blend (BDB), a mix of soil and compost materials comprising of a high microbial diversity. Sterilized BDB was provided in the cage bedding material of NOD mice 5 days/week, starting at weaning and until 9 weeks of age. Each exposure was carried out for 30 min in separate cages. Animals exposed to cage bedding material only served as controls. Fecal pellets were collected weekly and microbial composition measured by 16S sequencing and qPCR. Insulitis scoring was performed on formalin fixed pancreas sections. Exposure to the BDB was well tolerated. We observed a reproducible increase in *Lactobacilli spp.* in fecal samples and variable changes in T_{regs} in MLN in BDB-exposed mice. Insulitis scores were similar among groups. Our findings demonstrate that exposure to an inactivated natural material induces favorable shifts in the gut bacteria composition and could promote immunoregulation, without the need for live nature material or probiotics. Based on these novel observations and previous studies showing that it is safe to exposure human volunteers to BDB, we will next investigate whether BDB exposure can prevent experimental T1D.

Poster abstracts

P4 Stefan Norlin

O304 ameliorates hyperglycemia in mice by dually promoting muscle glucose effectiveness and preserving β-cell function

Stefan Norlin[1], Jan Axelsson[2], Madelene Ericsson[1], and Helena Edlund[1]

[1]*Umeå Centre for Molecular Medicine, Umeå University,*
[2]*Department of Radiation Sciences, Radiation Physics, Umeå University,*

Abstract
Although insulin mediated glucose uptake in skeletal muscle is a major mechanism ensuring glucose disposal in humans, glucose effectiveness, i.e. the ability of glucose itself to stimulate its own uptake independent of insulin, accounts for roughly half of the glucose disposed during an oral glucose tolerance test. Both insulin dependent and insulin independent skeletal muscle glucose uptake are however reduced in individuals with diabetes. We here investigate the effects of the AMPK activator O304 in insulin deficient mice, i.e. streptozotocin treated mice and db/db mice, showing that O304 stimulates insulin independent glucose uptake and utilization in skeletal muscle and heart *in vivo*, while preventing glycogen accumulation. Combined glucose uptake and utilization requires an increased metabolic demand and we show that O304 acts as a mitochondrial uncoupler, i.e. generates a metabolic demand. O304 averts gene expression changes associated with metabolic inflexibility in skeletal muscle and heart of diabetic mice and reverts diabetic cardiomyopathy. In Type 2 diabetes, insulin resistance elicits compensatory insulin hypersecretion, provoking β-cell stress and eventually compensatory failure. In db/db mice O304 preserves β-cell function by preventing decline in insulin secretion, β-cell mass, and pancreatic insulin content. Thus, as a dual AMPK activator and mitochondrial uncoupler O304 mitigates two central defects of T2D; impaired glucose uptake/utilization and β-cell failure, which today lack effective treatment.

Poster abstracts

P5 Maria Ovezik

Contribution of pancreatic macrophages to neonatal islet maturation and long-term glucose homeostasis.

Maria Ovezik[1], Carmen Herrera-Hidalgo[1], Kristel Parv[1], Sara Ullsten[1], Evelina Vågesjö[1], Haoyu Liu[1], Antoine Giraud[1], Per-Ola Carlsson[1,2], Gustaf Christoffersson[1,3], Mia Phillipson[1,3]

[1]*Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden;*
[2]*Department of Medical Science, Uppsala University, Uppsala, Sweden;*
[3]*The Science for Life Laboratory, Uppsala University, Sweden;*

Background and aim: Postnatal development of pancreatic islets to become competent at glucose regulation coincides with high densities of pancreatic macrophages, which are reduced as the islet function matures. Our aim is to investigate pancreatic macrophage contribution on islet maturation and the effect of neonatal infections in altering pancreatic macrophage numbers and increasing susceptibility for type 2 diabetes (T2D) later in life in mice exposed to normal or high fat diet (HFD).
Methods: C57Bl/6J mouse pups received *S.aureus* Xen29 bacteria or saline per orally at postnatal day 3 and 5. At weaning and onwards, the diet of some of the mice were changed to a HFD. Metabolic tolerance tests were performed on juvenile and adult mice along with weekly weight monitoring. Spleen and pancreas were weighed, pancreatic islets were immunostained and pancreatic macrophages ratio were analyzed. Protein expression in pancreatic macrophages was investigated in neonate and adult mice, and the role of macrophage-derived IGF1 (Insulin-like growth factor 1) was assessed using transgenic mice ($CX3CR1^{CreER}Igf1^{Flox/Flox}$) where *Igf1* was depleted specifically from the $CX3CR1^{+}$ macrophages by tamoxifen administration at postnatal days 1-7.
Results: Pancreatic macrophages of neonates contained higher IGF-1 levels compared to those from adults. Neonatal infections caused transient reduction of pancreatic macrophage numbers, resulted in reduced β cell proliferation and islet insulin content and impaired long term the ability to normalize glucose levels following challenge in mice exposed to normal or HFD. Impaired glucose tolerance was also demonstrated following macrophage-specific IGF1 depletion in young and adult mice.
Conclusions: These results demonstrate that neonatal pancreatic macrophages promote islet maturation by supplying IGF1, and that neonatal infections during the time of pancreatic islet maturation impair islet maturation and increase the risk for developing T2D.

Poster abstracts

P6 Ceren Incedal Nilsson

Acute and long-term somatostatin signalling via the β-cell primary cilium

T. Ceren Incedal Nilsson(1), Özge Dumral(1), Gonzalo Sanchez(1), and Olof Idevall-Hagren(1)*

(1) Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden

Primary cilia are microtubule-based organelles that protrude from the surface of β-cell. They are enriched for G protein-coupled receptors that enable the transduction of extracellular signals in parallel with canonical receptor signalling from plasma membrane receptors. The cilium offers alternative pathways for signalling. The hedgehog pathway requires functional cilia and is important for both pancreas development and maintenance of islet cell function in adulthood. Hedgehog-binding to its receptor Smoothened initiates Gi-dependent lowering of cilia cAMP and activation of GLI transcription factors. Other ciliary Gi-coupled receptors, as somatostatin receptor3, possibly contributes to this regulation. The aim of this study was to identify putative signalling pathways downstream of ciliary SSTRs. Immunostaining and confocal microscopy were used to determine the distribution of islet cell cilia and cilia-localized proteins in islets of Langerhans. Mouse islets and MIN6 pseudo-islets expressing a cilia-targeted cAMP sensor and TIRF microscopy was used to record ciliary cAMP dynamics. Addition of 100 nM somatostatin supressed forskolin-induced cAMP elevations in both cilia and cytosol; an effect was selectively diminished in cilia following siRNA-mediated knockdown of SSTR3 (control: 99±8% inhibition, siSSTR3: 54±7% inhibition, n=20, P=0.004), demonstrating that activation of ciliary SSTRs induce local changes in cAMP. Stimulation with somatostatin also evoked cilia-specific Ca2+ increases that were sensitive to pertussis-toxin treatment and suppressed following SSTR3 knockdown, showing that ciliary somatostatin signalling also involves Ca2+. Prolonged exposure to somatostatin (100 nM, 18h) or the Smoothened agonist SAG caused nuclear accumulation of GLI2 (control: 25%, Sst: 56%, SAG: 52%, Sst+SAG: 53%), indicating crosstalk between the somatostatin and Hedgehog pathways. Our results show that the primary cilium is a target of both acute and long-term somatostatin action in islets and indicate roles of somatostatin beyond acute inhibition of hormone secretion. Understanding these mechanisms will be important for understanding somatostatin-regulation of islet function in heath and diabetes.

Poster abstracts

P7 Neha Sinha

Mechanism of beta cell failure in diabetes and the associated single-cell gene expression change

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Abstract:
Background: Type 2 diabetes (T2D) is an escalating health problem of enormous proportions. Although existing drugs reduce hyperglycemia, they fail to stop the gradual beta-cell failure that is the key determinant of disease progression. There is consequently an urgent need for improved knowledge of the cellular mechanisms that cause beta-cell failure.
Aim: To investigate the gene expression changes in beta-cells of different functional pools.
Materials and methods: We used a new method to separate pools of low and high-responding beta-cells to glucose which enabled us to compare single-cell secretory function with gene expression using single-cell RNA-seq in both rodent and human tissue.
Results: Using single-cell RNA sequencing (scRNA-seq), we identified 157 genes that differ between function pools in non-diabetic and diabetic conditions. The genes are involved in pathways related to insulin secretion, dedifferentiation, membrane trafficking, and metabolic pathways.
Conclusion: Our study shows that scRNA-seq can be used to determine the cellular heterogeneity of the islet and to characterize the transcriptional profiles of individual cells. These findings provide new insights into the mechanisms underlying beta-cell failure. Moreover, scRNA-seq has facilitated the identification of rare subpopulations of cells that may be crucial in diabetes pathogenesis. By precisely defining the phenotype and proportion of cellular pools in both diabetic and non-diabetic conditions, we gain a more comprehensive understanding of beta-cell failure and potentially identify new targets to preserve beta-cell function, which is an urgent clinical requirement.

Poster abstracts

P8 Vijay Sai Josyula

The chemokine receptor CX_3CR1 as a major player in macrophage-nerve interactions in pancreatic islets.

Vijay Sai Josyula[1], Kevin Merchant[1], Elke Muntjewerff[1], Myrthe Reiche[1], Robin Lindsay[1], Gustaf Christoffersson[1,2].

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Objective- Increasing evidence points to an influence from pancreatic islet innervation in the onset of type 1 diabetes. Sympathetic nerves are known to influence immune cells mostly through noradrenergic signalling. Islet-resident macrophages express both α and β adrenergic receptors which skew the these into proinflammatory and anti-inflammatory nature respectively. Some tissue resident macrophages are known to be directly associated with sympathetic nerves. In the adipose tissue, nerve associated macrophages (NAMs) are in close association with the sympathetic nerves and aid in transport and degradation of excess norepinephrine. NAMs from various tissues were characterized by a high expression of the fractalkine (CX_3CL1) receptor CX_3CR1. We hypothesised that this receptor plays a major role in neuroimmune interactions in the pancreas and aimed to study this in mice.
Methods- Pancreatic sections were stained for tyrosine hydroxylase, a sympathetic nerve marker and F4/80 for macrophages and analysed for the volumes of the nerves and macrophages, and the surface-surface overlap between the two. A novel co-culture model was used to study the importance of CX_3CR1/CX_3CL1 expression in macrophages and/or neurons. Also, live imaging of pancreatic tissue slices was used to study the interactions between macrophages and T cells in a diabetes model at different stages of disease.
Results- Mice lacking CX_3CR1 had a reduced colocalization between macrophages and nerves. The co-culture model and the live pancreas slices further revealed the importance of this receptor for macrophage-nerve interaction in islets.
Conclusion- The data presented here hints to an involvement of CX_3CR1 in neuroimmune communication in pancreatic islets. Studying these interactions further in disease models could lead to possible pharmacological targets in treating autoimmune diabetes.

Poster abstracts

P9 Lina Matuseviciene

Paracrine signalling in delta cells of diagnosed human type-2 diabetics

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Introduction. In type-2 diabetes, paracrine regulation between islet cells is disturbed, but the underlying mechanisms remain unclear. **The aim** of this study was to quantify the effects of intra-islet signalling pathways on exocytosis in delta cells from non-diabetic (ND) and type 2 diabetic (T2D) human islets.
Methods. Live cell imaging was performed in pancreatic delta cells of ND (n=12) or T2D (n=5) cadaveric human donors. Delta cells were identified after transduction with adenovirus coding for granular marker under control of somatostatin promoter. Paracrine signalling was simulated by enriching cell medium with either of the following: insulin, glucagon, somatostatin, GABA, adrenaline, forskolin, or exendin-4. Exocytosis was then evoked by elevated K^+ in presence of glucose/ diazoxide and detected with TIRF (total internal fluorescence) microscopy. Somatostatin receptor 2 (SSTR2) expression was analysed by confocal microscopy of immunostained human pancreatic tissue sections.
Results. K^+-stimulated exocytosis of somatostatin granules followed a biphasic time-course in delta cells of T2D and ND donors. Autocrine somatostatin signalling led to auto-inhibition in ND delta cells (-60%, p=0.06), the effect no longer present in T2D. Similarly, adrenaline inhibitory effect on hormone secretion in ND (-76%, p=0.002) was reversed in diabetic cells (+12%, p=0.6). Glucagon, forskolin, excendin-4 and GABA were significantly increasing somatostatin secretion in both ND and T2D. Insulin did not affect delta cell exocytosis. Finally, reduced surface expression of SSTR2 in beta cells of T2D donors was observed.
Conclusions. We conclude that human delta cells are responsive to a variety of paracrine signalling pathways. In T2D, delta cells become resistant to inhibitory paracrine signalling while beta cells internalise its SSTR2 probably due to elevated somatostatin concentration within the islet.

Poster abstracts

P10 Özge Dumral

cGMP-dependent regulation of Ca^{2+} signaling in primary cilia of islet cells

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Cyclic nucleotides (cAMP and cGMP) are important modulators of insulin secretion that act through effector proteins, which are often compartmentalized within cells. One relevant compartment is the primary cilium, a microtubule-based organelle used for sensing the cellular environment that utilize cyclic nucleotides and Ca^{2+} as main signaling molecules. In the current project we use isolated mouse and human islets expressing subcellularly targeted biosensors for cGMP and Ca^{2+} to determine the relationship between these two molecules and ciliary signaling.
Atrial natriuretic peptide (ANP) can directly stimulate cGMP production. GC-A, the main ANP receptor, was expressed in both mouse and human islet cells. Stimulation of islets expressing the cytosolic cGMP sensor ScG1 with 500 nM ANP triggered a rise of cytosolic cGMP that was amplified by glucose, and the nucleotide readily diffused into the cilium, revealed by a cilia-targeted version of ScG1. The ANP-induced rise of cGMP was accompanied by pronounced Ca^{2+} influx in the primary cilia, but not in the cell bodies. The response was prevented by an ANP receptor antagonist and by siRNA-mediated knockdown of the cGMP-regulated Ca^{2+} channel CNGA3, which also showed pronounced cilia localization. cAMP, cGMP and Ca^{2+} can impact on each other at the level of phosphodiesterases (PDEs). Forskolin readily increased both ciliary and cytosolic cAMP, but did not trigger cGMP changes nor Ca^{2+} signaling. The subsequent addition of ANP lowered cAMP in both cytosol and cilia, possibly through increased PDE activity. This indicate that cGMP action may involve lowering of cAMP. The hedgehog pathway operates via the cilium and depends on lowering of ciliary cAMP and subsequent activation of GLI transcription factors. Consistently, we found that ANP induced nuclear entry of GLI2 to the same extent as the hedgehog pathway agonist SAG, indicating functional crosstalk between cAMP and cGMP signaling at the level of primary cilia.

Poster abstracts

P11 Erik Waara

ATTRACTIVE 1 - a first-in-human, dose escalating, double-blind, placebo-controlled trial of ATR-258 in healthy and type 2 diabetes participants

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Background and aims: Recent literature highlight the therapeutic potential of β_2-adrenoreceptor (β_2-AR) agonists to improve insulin sensitivity in humans with disturbed glucose homeostasis. ATR-258 is a new small molecular compound, targeting the β_2-AR in a novel way, leading to stimulation of glucose uptake in skeletal muscle, independently of the insulin signaling pathway. The primary objective of this trial is to evaluate the safety, tolerability, and pharmacokinetics (PK) after oral dosing with ATR-258. **Materials and methods:** During single ascending dose (SAD) escalation, altogether 22 male HVs received 0.5-10 mg ATR-258 or placebo. In the multiple ascending dose (MAD) escalation, altogether 24 male HVs received ATR-258 or placebo over 7 days. In part C, 24 male TD2 patients received 2.5 mg ATR-258 or placebo over 28 days. In the T2D patients, pharmacodynamic variables such as HbA1c, fasting glucose and insulin, glucose tolerance and continuous glucose monitoring are collected. Biomarker (pancreatic, kidney, liver and obesity) and magnetic resonance imaging (MRI) assessments are performed. **Results:** ATR-258 is safe and well tolerated, based on the blinded safety data from the HVs. Adverse events (AE) observed in the HVs were mild and transient, such as headache, palpitations and restlessness. Blinded ECG data illustrates transient heart rate (HR) elevation. Plasma PK analysis after single and multiple ATR-258 dosing suggests fast absorption with a plasma half-life of 10 hours. **Conclusion:** ATR-258 targets the β2-AR signaling pathway, leading to the stimulation of glucose uptake in skeletal muscle. Preliminary blinded safety data from HVs suggest that oral treatment with ATR-258 is safe and well tolerated and has a favorable plasma half- life. If successful, ATR-258 could be the first of a new class of anti- diabetic drugs, with presumably better safety profile, potentially presenting an attractive and an efficient option to T2D patients.

Poster abstracts

P12 Kirstin MacGregor

Integrated analysis of the Skeletal Muscle Transcriptome and Methylome in Response Exercise Reveals Distinct Differences Between Females with Type 2 Diabetes and Normal Glucose Tolerance

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Epigenetic modifications through DNA methylation contribute to the control of skeletal muscle metabolism. We examined whether exercise induces distinct skeletal muscle transcriptional and methylation profiles in females with normal glucose tolerance (NGT) or type 2 diabetes (T2D). Females with T2D (N=19) or NGT (N=14) completed a 60 min exercise bout on a cycle ergometer at 85 % maximal heart rate. Vastus lateralis muscle biopsies were collected before (pre), immediately after (post) and 3 hr after exercise (recovery). Total RNA and DNA were isolated from biopsy tissue to perform transcriptome and methylation arrays. A quantitatively larger transcriptional response was observed in females with T2D at recovery vs pre, with 3,839 genes unique to this group. Differentially expressed genes (DEG) were positively enriched in pathways related to antigen processing and presentation in females with T2D at recovery vs post and recovery vs pre, but only in females with NGT at recovery vs post. Females with T2D had a greater number of differentially methylated sites (N=11,187) and differentially methylated regions (DMR) (N=3,143) at recovery vs pre. Pathway analysis using differentially methylated CpG sites identified similar pathways enriched in response to exercise in both disease groups relating to lymphocyte and leukocyte function, immune response, and antigen signalling. The intersection between DMRs and DEGs was similar in both diagnoses groups at recovery vs post, with 6-10 % DMRs common to DEGs. However, 25 % (N=922) of DMRs were common to DEGs in females with T2D at recovery vs pre. Associations between DMR mean difference and DEG fold change was quantitatively greater in females with T2D at recovery vs pre, where associations between 108 unique genes were identified. Thus, skeletal muscle epigenomic and transcriptomic response to exercise differs between females with T2D and NGT, with a heightened "*immunometabolism"* signature emerging in response to exercise with T2D.

Poster abstracts

P13 Maxence Jollet

Upregulation of diacylglycerol kinase delta contributes to improve glucose clearance and resistance to obesity

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Type 2 diabetes (T2D) mellitus is a progressive metabolic disease that impairs glucose metabolism in different tissues. We previously reported that diacylglycerol kinase delta (DGKδ) expression and activity is reduced in skeletal muscle from type 2 diabetic patients. Interestingly, exercise training has been shown to increase DGKδ in skeletal muscle from diabetic and non-diabetic patients. DGKδ haploinsufficient mice have impaired peripheral insulin sensitivity, insulin signaling and glucose transport associated with metabolic flexibility. To further explore the metabolic role of DGKδ, we generated a transgenic mouse model overexpressing the human DGKδ isoform mainly in skeletal muscle. We highlighted a leaner phenotype in DGKδ TG mice associated with a faster glucose clearance independent of insulin sensitivity, partially driven by the increase of glycogen storage in EDL. Interestingly, white adipocytes from DGKδ TG mice were smaller, lighter and their lipolysis capacity was increased. DGKδ TG mice are protected from obesity induced by 12 weeks of high fat diet (HFD) associated as evidenced by improved glucose tolerance with a trend for enhanced insulin sensitivity. Strikingly, DGKδ overexpression replicates the positive exercise effects on metabolic outcomes. Indeed, sedentary DGKδ TG mice phenocoped exercise-trained WT mice. Moreover, even on HFD, DGKδ TG mice phenocoped exercise-trained WT mice. Microarray analysis of EDL muscle confirmed these findings and highlighted the synergy of DGKδ overexpression and exercise training to preserve glucose metabolism. We confirm the key role of DGKδ in metabolic regulation, whereby overexpression induces changes in both skeletal muscle and adipose tissue, resulting in protection from HFD-induced obesity. Beneficial effects of DGKδ overexpression on metabolism partly mimic the effects of exercise training.

Poster abstracts

P14 Ben Stocks

The deubiquitinase UCHL1 is downregulated in the liver of men with type 2 diabetes and regulates mitochondrial metabolism

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Dysregulated liver metabolism, in particular insulin resistance, is a predominant factor in the pathogenesis of type 2 diabetes. Protein degradation via the ubiquitin-proteasome system has been implicated in the development of type 2 diabetes. Through a diversity of signals, ubiquitination regulates a range of cellular processes such as protein degradation, enzyme activation and sub-cellular localisation. We aimed to characterise the regulation of the ubiquitin-proteasome system in the liver of severely obese men with and without type 2 diabetes.
Liver samples from 9 non-obese men, 8 severely obese men (Ob) and 10 severely obese men with type 2 diabetes (Ob-T2D) were collected during cholecystectomy (non-obese) or Roux-en-Y gastric bypass surgery (Ob and Ob-T2D). Samples were lysed in 4% SDS and digested using Lys-C and trypsin. Peptides were measured via liquid chromatography tandem mass spectrometry (LC-MSMS) using an EASY nanoLC coupled to an Exploris 480 Orbitrap on a 100-min gradient using data independent acquisition. Protein ubiquitination was assessed via immunoblotting in human and rodent liver.
We identified the regulation of 4319 proteins in the livers of 9 non-obese, 8 severely obese non-diabetic men (Ob) and 10 severely obese men with type 2 diabetes (Ob-T2D), collected during cholecystectomy (non-obese) or Roux-en-Y gastric bypass surgery (Ob and Ob-T2D). We found 162 proteins that were differentially regulated in Ob and/or Ob-T2D compared to non-obese men. Of these, 11 ubiquitin-proteasome system proteins were regulated, including the deubiquitinase UCHL1, which was concomitant with an increase in protein ubiquitination. Knockdown of UCHL1 in human hepatocytes (Huh7 cells) decreased mitochondrial oxygen consumption rate, indicating reduced hepatic mitochondrial respiratory capacity with loss of UCHL1. These data identify ubiquitin-proteasome system dysfunction in the liver of severely obese men with and without type 2 diabetes, providing protein targets for future mechanistic and therapeutic research.

Poster abstracts

P15 Sara Torstensson

Altered immune populations in adipose tissue of a normal weight mouse model of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder, characterized by high circulating androgen levels and with a strong link to metabolic comorbidities, where 50% of women with PCOS develop type-2 diabetes (T2D) before the age of 40. Immune cells residing in adipose tissue play a central role in glucose homeostasis, and a low-grade inflammation is associated with PCOS as well as T2D. To determine how hyperandrogenism affects the immune populations in visceral adipose tissue (VAT), we characterized the immune profile of the dihydrotestosterone (DHT)-induced PCOS-like mouse model, with or without co-treatment with flutamide, an androgen receptor (AR) antagonist.

To assess if DHT-exposed mice (PCOS-mice) develop a metabolic phenotype, body composition was analyzed by EchoMRI, and glucose metabolism was assessed by oral glucose tolerance test and HbA1c. While no effect was seen on fat mass, PCOS-mice displayed higher insulin levels following challenge and elevated HbA1c. Next, the immune profile in VAT was analyzed by flow cytometry. The number of eosinophils in VAT was drastically reduced in PCOS-mice compared to controls. Multiplex analysis showed decreased IL-5 in VAT, which could affect the survival of eosinophils. Moreover, NK cells in VAT of PCOS-mice displayed a higher expression of CD69, a marker of activation or tissue residency. Levels of IFN-γ were lower in VAT of PCOS-mice, contradicting a higher activation state of NK cells. Finally, macrophages in VAT of PCOS-mice displayed an altered phenotype, with lower MHC-II expression and higher expression of CD11c compared to control. All effects of DHT exposure were prevented by co-treatment with flutamide, showing that the observed alterations are AR driven.

These findings show that androgen exposed mice develop insulin resistance with altered immune populations in visceral adipose tissue, independent of fat mass. If these alterations are underlying the higher susceptibility to metabolic dysfunction in PCOS remains to be elucidated.

Poster abstracts

P16 Giovanni Solina

Adipocyte PI3K Links Adipostasis with Basal Insulin Secretion Through an Adipoincretin Effect

Short title: Adipocyte PI3K Controls Fasting Insulin and Adipostasis

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Insulin secretion is governed by insulin-PI3K signaling. Resolving the mechanism of this feedback is necessary to understand how insulin operates. Adipose tissue-specific knockout mice for the insulin receptor, or AKT1 and AKT2, are severely lipoatrophic. Thereby, the role of adipocyte insulin signaling in the feedback control of insulin secretion remains unknown. Using adipocyte-specific PI3Kα knockout mice ($PI3K\alpha^{AdQ}$) and a panel of isoforms-selective PI3K inhibitors, we have found that PI3Kα and PI3Kβ are functionally redundant in adipocyte insulin signaling. PI3Kβ-selective inhibition blunted adipocyte AKT phosphorylation and increased serum FFA and insulin secretion in $PI3K\alpha^{AdQ}$ mice but not in control mice. We name this phenomenon the adipoincretin effect. The adipoincretin effect was induced in mice fasted overnight with decreasing glycemia. The effects of adipocyte-specific PI3K inhibition on insulin secretion and serum FFA could be partly dissociated by cotreating $PI3K\alpha^{AdQ}$ mice with nicotinic acid. We conclude that, during fasting, insulin secretion and lipolysis are coregulated by adipocyte PI3K signaling through the adipoincretin effect.

Poster abstracts

P17 Leo Westerberg

Western Blot Accuracy in Mature Human Adipocytes: Embracing Total Protein Normalization

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** Indicates equal contribution to the study*

Since the late 1970s, western blotting has been a cornerstone method for protein expression analysis. However, despite its widespread use, a consensus on the most appropriate normalization approach has yet to be established. In this project, our primary objective was to investigate the choice between housekeeping proteins and total protein as normalization references in western blotting using primary mature human adipocytes. First, we compared variance in technical replicates, this revealed total protein to be more stable than all housekeeping proteins investigated. Next, we assessed the dynamic range of our different normalization references by employing a loading gradient approach. Total protein closely aligned with the expected value for each loading amount, making it a robust choice for normalization. Lastly, we examined three metabolically similar cases, gauging the performance of different normalization references when comparing different individuals. Notably, we observe substantial differences in housekeeping protein expression among patients, making them unsuitable as normalization references in cohorts of biological samples. In conclusion, we strongly recommend total protein normalization over housekeeping protein normalization for western blotting using primary human adipocytes.

Poster abstracts

P18 Niels Krämer

White fat cell volume associates with reduced UCP1$^+$ adipocytes in human brown fat depots

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Background
Brown adipose tissue (BAT) is a potential target for the treatment of obesity. However, despite important previous studies, the prevalence of BAT, as defined by uncoupling protein 1 (UCP1) expression, is unknown in adult humans.
Methods
BAT was sampled from 7 putative BAT depots from 65 *post-mortem* cases. This was followed by random systematic sampling and staining for UCP1. Adipocyte area fraction (AF) was assessed and its association with BMI, donor age, temperature, sex and white adipocyte size determined using hurdled negative binomial regression.
Results
UCP1$^+$ adipocyte AF was small in all depots (1-10%), with large variation seen across individuals. Increased white adipocyte cell size correlated negatively with UCP1+ AF. When the effects of white adipocyte size, age, BMI, sex and temperature on UCP1$^+$ adipocyte AF were assessed, the canonical negative associations of both age and BMI were mostly mediated via white adipocyte size.
Conclusion
Human BAT depots consist mostly of white adipocytes, with the AF of UCP1$^+$ cells mostly depending on the depot and local white adipocyte size.

Poster abstracts

P19 Alice Maestri

A novel *in vitro* model to study lipid droplet dynamics in white adipocytes: Human Unilocular Vascularized Adipocyte Spheroids (HUVAS)

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Background:
Obesity and its consequences are a rising pandemic with the white adipose tissue, the principal lipid storing organ, being heavily affected. Adipocytes contain unilocular lipid droplets with ranging diameter of 65 um in the lean state, to over 200 um in the obese. Besides enlarging in size, the cells also become dysfunctional. *In vitro* models, both 2D and 3D, are used to study the biological features of adipocytes but lack the classical white adipocyte lipid droplet unilocularity, stressing the need for further development. We present the **Human Unilocular Vascularized Adipocyte Spheroid (HUVAS)**, a novel 3D model which enables the study of human unilocular adipocyte biology and its lipid droplet dynamics *in vitro.* This model can also be used to study adipocytes during obesity since we are able to fatten and enlarge the cells.

Results:
By providing a growth niche consisting of endothelial sprouts and extracellular matrix, we improved the *in vitro* preadipocyte differentiation to a level that permits cells to reach maturation, lipid droplet unilocularity and adipokine secretion comparable to mature adipocytes.
By removing the vasculature via omitting the extracellular matrix, which enables vascular sprouting, or by inhibiting angiogenesis via a continuous treatment with an anti-VEGF-A antibody, we reported no impairment in adipocyte differentiation, but loss of lipid droplet unilocularity, impaired adipokine secretion and a shift in metabolism. Through the manipulation of mitochondrial activity, we were able to alter the level of unilocularity in our system, suggesting that adipocytes' mitochondrial activity, supported by the presence of vascular endothelial cells, promotes healthy adipocyte lipid storage.

Conclusions:
HUVAS is a human 3D adipose tissue model able to recapitulate key features of the white adipose tissue. By manipulating our system, we elucidated the importance of adipocyte-endothelial interactions for adipocyte maturation, discovering it is fundamental for the generation of unilocular lipid droplets.

Poster abstracts

P20 Julia Sánchez-Ceinos

Endothelial-specific deletion of lysine methyltransferase SET7 protects mice from obesity and insulin resistance-related endothelial dysfunction

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We have previously reported that the lysine methyltransferase SET7 is implicated in the high glucose-induced endothelial damage in subjects with type 2 diabetes through mono-methylation of histone 3 at lysine 4 (H3K4me1). Apart from such histone-driven epigenetic modulation, SET7-mediated methylation of non-histone proteins is emerging as a novel mechanism underlying the (dys)regulation of several biological processes. Here, we investigate the dual role of SET7 in endothelial dysfunction in obesity and IR.

Thus, both wild-type mice and mice with a specific genetic deletion of Set7 in the endothelium ($Set7^{EC\text{-}KO}$) were subjected to either normal or high-fat diet (HFD). Despite similar obesity and IR phenotypes, aortas from $Set7^{EC\text{-}KO}$ mice were protected against HFD-induced poor endothelium-dependent relaxation. *In vitro* experiments using human aortic endothelial cells (HAECs) revealed that the exposition to high concentrations of glucose increases the expression levels of SET7. Significant changes in the global patterns of H3K4me1, as well as of Kme1-proteins were also observed in this condition. Additional studies overexpressing an active or an inactive form of SET7 (lacking the SET domain) demonstrated that SET7´s methyltransferase activity is crucial in defining the protein methylome at both histone and histone-protein levels in HAECs. Also, this activity appears to trigger oxidative stress and inflammation in these cells. Similar results were obtained when SET7 was silenced using specific siRNA or inhibited by cyproheptadine. Finally, proteomics analysis of the whole proteome and Kme1-proteins allowed us the identification of potential target proteins of SET7. Interestingly, these proteins were found to be involved in alternative splicing and eNOS signaling pathways.

Taken together, our findings suggest that SET7 may contribute to endothelial dysfunction in obesity and IR, primarily through inflammation and oxidative stress induced by hyperglycemia. Moreover, our results uncover a dual role of this lysine methyltransferase in modulating both histone and non-histone proteins in endothelial cells.

Poster abstracts

P21 Jasmin Swaich

Red blood cell-derived extracellular vesicles induced vascular endothelial injury in type 2 diabetes through increased oxidative stress

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Background
We recently demonstrated that red blood cells (RBCs) from patients with T2D (T2D-RBCs) induce endothelial dysfunction. It is increasingly clear that extracellular vesicles (EVs) are actively secreted by RBCs and represent a novel mechanism of intercellular communication.

Purpose
This study aims to investigate oxidative stress as one of the possible mechanisms by which RBC-derived EVs induce endothelial dysfunction in T2D.

Material and Methods
EVs isolated from T2D-RBCs and H-RBCs were incubated with wild-type mice aortas for evaluation of the endothelial function with the presence or absence of N-acetyl cysteine (NAC; 10 mM) during the 18h co-incubation or to the aortas (100 μM) to selectively target vascular oxidative stress. The levels of the oxidative stress marker 4-hydroxynonenal (4-HNE) and phospho-eNOS were quantified by immunohistochemistry in aortas incubated with EVs. Additionally, T2D-RBCs EVs and H-RBCs EVs were incubated with human carotid endothelial cells (HCtAEC) for 8h and 24h to study altered expression levels of eNOS, NOX1, and NOX4 using qPCR.

Results
Immunohistochemistry showed a significant increase in 4-HNE and phospho-eNOS levels in those aortas incubated with T2D-RBCs EVs. T2D-RBCs EVs induced endothelial dysfunction in mice aortas, which was reversed by the addition of NAC in the vessel, but no changes were observed when applied during the co-incubation. Additionally, co-incubation between HCtAEC and EVs showed a significant increase in NOX4 when incubated with T2D-RBCs EVs after 24h while not after 8h. There were no significant differences in eNOS and NOX1.

Conclusion
EVs derived from T2D-RBCs induce endothelial dysfunction through increase oxidative stress.

Poster abstracts

P22 Aida Collado

Erythrocyte-derived extracellular vesicles from type 2 diabetes patients induce endothelial dysfunction through arginase 1

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Introduction: The mechanisms driving the development of cardiovascular injury in type 2 diabetes (T2D) remain incompletely understood. We recently demonstrated that red blood cells (RBCs) from patients with T2D (T2D-RBCs) act as mediators of endothelial dysfunction, but the mechanisms remain unclear. It is increasingly clear that extracellular vesicles (EVs) are actively secreted by practically all cell types, including RBCs, and represent a novel mechanism of intercellular communication. **Purpose:** This study aimed to determine whether EVs derived from T2D-RBCs are involved as mediators in vascular injury through the signaling of arginase-1. **Material and Methods:** EVs were isolated from T2D-RBCs and healthy RBCs (H-RBCs) and co-incubated with endothelial cells for 24h to study the uptake or with mouse aortas for 18h for evaluation of endothelial function with the presence or absence of heparin to block the uptake of EVs and arginase inhibitor (ABH). Immunohistochemistry was performed on aortas incubated with EVs for levels of arginase. **Results:** We demonstrated that T2D-RBCs released 50% fewer EVs than healthy controls. However, the uptake of T2D-RBCs EVs by endothelial cells was significantly greater than that of EVs from H-RBCs. These EVs induced endothelial dysfunction in mouse aortas, which was reversed by the addition of ABH and heparin. Immunohistochemistry showed that arginase-1 is increased after incubation with T2D-RBCs EVs. **Conclusions:** EVs derived from T2D-RBCs induce endothelial dysfunction through arginase-1. These results shed new important light on the mechanism underlying vascular injury mediated by RBCs in T2D.

Poster abstracts

P23 Eftychia Kontidou

Duration of diabetes promotes the erythrocyte-induced endothelial dysfunction: a link to mir-210?

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Background: Type 2 diabetes (T2D) is an important risk factor of cardiovascular complications. Endothelial dysfunction plays a major role in the etiology of T2D-induced vascular injury. We recently demonstrated that miR-210 levels in erythrocytes (RBCs) from T2D patients are decreased, which contributes to the development of endothelial dysfunction.
Aims: To investigate the effect of T2D duration on endothelial dysfunction induced by RBCs and whether this is associated with the RBC miR-210 levels.
Methods: RBCs were isolated from wild-type mice (14 or 22 weeks) or from T2D db/db mice with different ages (7, 14 or 22 weeks). RBCs (hematocrit: 45%) were incubated with aortic segments from wild-type mice (14 weeks). Following 4h incubation, endothelium-dependent relaxation (EDR) was evaluated on the aortic segments using wire myograph and miR-210 levels were measured in the RBCs by qPCR.
Results: db/db mice at all ages exhibited higher blood glucose levels compared to wild-type mice. Interestingly, EDR was impaired in vessels incubated with RBCs from db/db mice with age of 14 and 22 weeks to a similar extent, while EDR was preserved in vessels incubated with RBCs from db/db mice at age of 7 weeks. Of note, miR-210 expression levels were significantly decreased in the RBCs from db/db mice with ages of 14 and 22 weeks compared to those from db/db mice with age of 7 weeks.
Conclusions: Duration of T2D in mouse model appears to play a role in endothelial dysfunction induced by RBCs, and this is likely associated with the miR-210 levels in RBCs.

Poster abstracts

P24 Glykeria Karadimou

Repression of CHIT1 and osteoclast formation regulates increased calcification in atherosclerotic plaques of diabetic patients

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The pathophysiology behind aggravated atherosclerosis in diabetes is incompletely understood. We hypothesized that transcriptomic analysis of plaques from type 2 diabetic patients (T2D) can reveal molecular mechanisms common between diabetes and atherosclerosis.

The Biobank of Karolinska Endarterectomies (BiKE) comprises plaques and clinical data from patients undergoing endarterectomy for carotid stenosis, profiled with whole-genome transcriptomic arrays. Bioinformatic analyses of differentially expressed genes were performed comparing plaques from patients with T2D (n=30) vs. non-T2D (n=39). Patients were stratified in two groups according to HbA1c levels (HbA1c <4.9%) and existing diabetes diagnosis.

In plaques from diabetic vs. non-diabetic atherosclerotic patients, the most affected pathways were related to metabolic, coagulation, calcification, and cell trans-differentiation processes. CHIT1 protease was one of the most repressed transcripts specifically in plaques from T2D ($p<0.0001$). CHIT1 expression was associated with macrophages, extracellular matrix and markers related to ossification processes. Immunohistochemical staining revealed co-localization of CHIT1 and CD68 in multinucleated cells resembling osteoclasts. Spatial transcriptomic analysis of plaques revealed a 7-fold increase in CHIT1 expression in multinucleated cells compared to other regions of interest. Typical osteoclast markers were upregulated in these multinucleated cells compared to areas populated by smooth muscle cells and macrophages. *In vitro* differentiation of human PBMCs to osteoclasts, revealed decreased osteoclast formation under hyperglycemic conditions.

Our findings reveal induction of stabilization processes related to ossification in plaques from T2D. CHIT1 was identified as one of the novel genes expressed by plaque osteoclasts, which repression appears to distinguish atherosclerotic plaques from T2D and is currently being investigated mechanistically.

Poster abstracts

P25 Roger Chang

Proteomic Indicators of Metabolic Health in Diabetes and Social Deprivation

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Aim: Understanding the intricate interplay between socioeconomic deprivation (SED) and its interaction with type 2 diabetes (T2D) is pivotal for optimizing patient care and devising effective public health strategies. The SomaScan Assay, an aptamer-based technology capable of measuring 7000 blood proteins. SomaSignal Tests (SST), machine learning algorithms, were developed from 180 million proteomic measurements from 26,000 participants across eleven clinical studies. SSTs recognize changes in proteomic patterns that are associated with various health statuses and lifestyle factors.
Method: We employed SomaScan Assay and 10 cardiometabolic SSTs to estimate levels of visceral fat, lean body mass, liver fat, body fat percentage, resting energy rate, cardiorespiratory fitness, glucose tolerance, alcohol impact, kidney health, and more importantly a SST that predicts risk of cardiovascular (CV) event within 4 years on participants in the PsoBid study. Participants were recruited from SED and affluent areas of Glasgow, Scotland with similar age ranges and equal proportions of male and female, to identify relevant health disparities. Linear regression analyses were used to estimate the association between proteomic signatures and socioeconomic status (affluent (n=257, 50.7%), SED (n=250, 49.3%)) and prevalent diabetes (n=27 (5.3%); 7 (2.7%) affluent and 20 (8.0%) SED).
Results and conclusions: Our findings show that participants with diabetes or from SED areas have proteomic phenotypes consistent with decreased cardiometabolic health status compared to those without diabetes or from affluent areas. Moreover, the increased risk of developing a CV event is strongly linked with diabetes and wealth disparity. Furthermore, we demonstrate that proteomics offers valuable information to aid in identifying and monitoring the cardiometabolic health status of T2D patients and individuals residing in SED areas. This approach holds potential for enhancing diagnostics, interventions, and deepening our understanding of the complex interplay between health, disease, and socioeconomic status.

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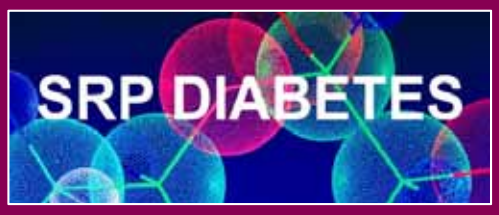

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